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PUBLIC TESTIMONY ON ASSEMBLY BILL 506 AND SENATE BILL 354

Joint Public Hearing of the Assembly Public Health Committee and Senate Committee on Health, Health Insurance, Privacy, Property Tax Relief, and Revenue
October 22, 2009

Thank you to the committees for hearing these companion bills today. I concur with what Senator Erpenbach has just said, and would add that as a neurologist who has treated many patients with seizure disorders, I understand the necessity of maintaining tight control of blood levels of anti-epileptic medications.

Should the level drop too low, there is the risk of breakthrough seizures which could lead to injury of the patient, or others around them should he or she be driving. A breakthrough seizure can also mean loss of driving privileges, and possible loss of employment opportunity.

If the blood level gets too high, above the therapeutic range, then dizziness, lethargy, visual disturbances, slurred speech, imbalance, and other toxic side effects can occur.

Once a patient is stabilized on a certain formulation of their anti-epileptic medication, it is important to maintain that same formulation, whether it is a brand-name or a generic. <u>It is the consistency of the formulation that is important.</u> Various generics should all contain the same amount of active

medication, but can vary in their inert ingredients, which makes up the bulk of the pill; and different inert ingredients can lead to differing undesirable results.

For example, if the inert material dissolves rapidly in the stomach, the medication will be released quickly, possibly leading to a toxic side effect. If the inert material dissolves too slowly, it could allow the blood level to drop below the therapeutic range, which could result in a subsequent breakthrough seizure.

Passage of these bills should help the patient with a seizure disorder by encouraging the consistent use of anti-epileptic medication formulations, and being sure the prescribing practitioner and the patient, or the patient's agent, is informed of any necessary change.

I encourage your support for Assembly Bill 506 and Senate Bill 354.

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Testimony from Pharmacy Society of Wisconsin

Before the Assembly Committee on Public Health and the Senate Committee on Health Senate Committee on Health, Health Insurance, Privacy, Property Tax Relief, and Revenue

Assembly Bill 506 and Senate Bill 354

Tom Engels, Vice President of Public Affairs

Thursday, October 22, 2009

Thank you Chairman Benedict and Members of the Assembly Committee on Public Health and Chairman Erpenbach and members of the Senate Committee on Health Senate Committee on Health, Health Insurance, Privacy, Property Tax Relief, and Revenue for the opportunity to testify on the legislation before you today.

The Pharmacy Society of Wisconsin (PSW) represents over 3,000 pharmacists and pharmacy practices in the state. We are pleased to offer the following commentary regarding the treatment of epilepsy with prescription medications.

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The legislation before you today would reduce the use of generic medications in the treatment of patients in Wisconsin with epilepsy. It would not change how patients are treated, it would not improve health care quality, and it would not change insurance coverage requirements. It simply would place additional administrative hoops on the use of generic medications, causing increased costs and lessened efficiency.

The issue of whether a generic drug is equivalent to a brand-name medication is at the heart of this legislative debate. Proponents of bills to make substitution more difficult emphasize that AB-rated drugs (as determined by the FDA) could have a bioequivalence difference of as much as 20%, too great a range for a complex disease like epilepsy, they caution. But in the Food & Drug Administration's bioequivalence report, generic antiepileptic drugs range from 2-5 %. The FDA has repeatedly stated that there is no evidence of problems with the bioequivalence of generic antiepileptic medications—none. Even a committee of experts convened by the National Epilepsy Foundation in 2006 agreed that there was no authoritative evidence of generic medications causing problems in the treatment of epilepsy.

FDA further advises that it is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class when there has been a determination of therapeutic equivalence, as is the case for all approved generic medications. Any state that passes generic carve-out legislation would, in effect, be inappropriately inserting itself into what is the proper domain of the FDA—the regulation of drug safety.

Anti-generic substitution legislation was introduced in more than 30 states during the last legislative session. A similar pattern is re-emerging this session, after mass rejection by state legislatures the last time around. Not coincidentally, during the same time period, over $5 billion in brand name drugs were becoming available generically as their patents expired. Also not coincidentally, the state legislative initiatives, including the one here in Wisconsin, are being funded by brand name pharmaceutical companies eager to either regain or retain market share.

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Restricting the use of generic medications in Wisconsin would cost taxpayers and health plans tens of millions of dollars, putting even greater pressure on prescription drug program budgets. These increases would come at a time everyone is seeking solutions to reign in costs and improve the quality of care. A report prepared for the Pharmaceutical Care Management Association projected legislation such as what is being considered today would increase costs by more than $300 million—in Wisconsin!

It is also important to understand, when a patient, pharmacist or physician has concern about an individual patient using a generic medication, there is authority to use a brand-name medication today, without any change in state law. A physician can mark an individual prescription order "Brand Medically Necessary" and the patient will receive the designated brand name product. Similarly, a patient can request a brand name product from their pharmacist at any time. Insurance plans may not pay for the brand name product, if it is not deemed medically necessary; however, every patient is legally allowed to receive the brand name medication. The legislation under consideration does not obligate insurance companies to change their coverage policies for branded products; therefore, patients would incur increased costs when requesting brand name medications, regardless of the passage of this proposal.

Questions have also been raised regarding potential problems when pharmacies change manufacturers of generic medications—in particular when a patient receives a medication made by a different generic manufacturer at the time of receiving a refill. Although there is no evidence that switching from one generic manufacturer to another has created problems, and while there are legitimate reasons a pharmacy will change generic manufacturers, PSW recommends maintaining consistency of generic manufacturers by pharmacies to lessen patient confusion and concern. Sometimes the same generic medications, made by different manufacturers, have different colors, shapes and sizes. Sometimes such changes cause confusion and it is important for pharmacists to explain to patients whenever a change in manufacturer has occurred. However, all AB-rated generic medications are required to meet the same bioequivalence standards by the FDA; therefore, there should be no significant deviation from one generic to another.

Lastly, not only is the proposed policy not necessary and certain to increase spending on prescription drugs, it will create a new and higher level of inefficiency in the system. Pharmacists would be required to call the physician and receive his or her consent to use a generic medication if the patient prefers the less expensive alternative or if their health insurer determines the branded medication not to be medically necessary.
This requirement would result in thousands of unnecessary phone calls from Wisconsin pharmacists to Wisconsin physicians each month. The physician would be required to personally provide the consent. If a particular physician can not be found or reached for their consent, the patient would have to pay the higher price for the branded medication or delay therapy until the physician is reached. Neither of these results is good for the patient and each will add inappropriate administrative cost to the dispensing of a prescription.

If you would like to do something to improve the quality of care for patients with epilepsy, we encourage you to adopt policies that would fund intensive medication therapy management for the patients that need the most assistance. Initiatives like the Wisconsin Pharmacy Quality Collaborative (WPQC), designed to engage a patient's caregivers in a coordinated and meaningful manner is what is needed. Both brand and generic medications are proven therapies--let's make sure that we are getting the greatest value possible by ensuring that all medications are used properly.

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I have attached two additional papers to this testimony for your reference; the first is PSW's issue paper on AB 506 and SB 354 that provides more detail of the information presented by our testimony. The second paper is an Executive Summary of the WPQC program.

In conclusion, we respectfully request that you turn down this legislative proposal. While the intent of the proponents of this legislation is understandable, the negative consequences associated with the passage of this legislation are profound.

Thank you for this opportunity to present to you on behalf of the state's pharmacy practitioners. I would be pleased to answer your questions.

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Issue Brief

Substitutions by Pharmacists Dispensing Epilepsy Drugs

State Representative Chuck Benedict (D-45) and State Senator Jon Erpenbach have introduced legislation at the request of the Epilepsy Foundation that would prohibit the generic substitution of prescription medications used for the treatment of epilepsy without the expressed consent of both the prescriber and patient. The legislation was introduced simultaneously in both the Assembly and Senate, the bill numbers are Assembly Bill 506 (AB 506) and Senate Bill 354 (SB 354).

Background

Based on the provisions of bills, a pharmacist would be prohibited from substituting an equivalent generic medication for its brand counterpart and from substituting a generic medication from one manufacturer for an equivalent generic medication made by another manufacturer, for all prescription products used in the treatment of epilepsy. A substitution would only be allowed with the documented consent and authorization of both the prescribing practitioner and the patient (or the patient's spouse, parent or legal guardian). This is similar to legislation introduced last session by Senator Erpenbach.

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Generic Substitution in Wisconsin

As it relates to interchange of prescription drug products, Wisconsin has taken a common and conservative approach that relies upon a sophisticated therapeutic equivalency testing process of the Food and Drug Administration (FDA). In Wisconsin, medications available for generic substitution only include those that meet the most rigorous equivalency tests that receive the FDA's A/B rating. Wisconsin pharmacists work everyday to help patients in their medical treatments and help to reduce the cost of prescription medications by dispensing lower cost generic medications. In fact, Wisconsin law requires pharmacies to dispense a therapeutically equivalent generic prescription drug, if it is lower in cost, unless a patient requests a brand name product. This practice has been proven to help lower the cost of health care while maintaining the quality of treatment.

There are some instances where a prescribing practitioner will request that a specific medication be dispensed to a patient. In that case the prescribing practitioner will indicate that directive by writing "dispense as written" (DAW) on the prescription order. When DAW is written on a prescription order and the medications are dispensed by a pharmacist, that medication order cannot be changed without a change by the prescribing practitioner. Most insurers and health plans provide a system for such a product to be considered for approval, dispensing and reimbursement.

Unintended Consequences

It is common for a pharmacy or the pharmacy's wholesale distributor to change sources of generic products based upon the availability of the product and pricing

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advantages from one manufacturer over another. Changes in generic supply can change literally every month. It is possible that a patient would be unable to locate a pharmacy that stocks the very same generic manufacturer's product. Therefore, if one pharmacy's generic supplier changed, it is possible that a patient would be unable to locate a pharmacy with a supply of the generic medication from the first generic manufacturer. Patients would also be set-up for failure as they are admitted or discharged from a hospital that may stock a different generic manufactured product than what the patient had received from a community pharmacy. Further, generic medications cost about ¼ of the brand-name medication cost, on average, although the difference varies from medication to medication.

If enacted, this legislation will result in lower use of generic medications, resulting in higher health care costs — for epilepsy patients, businesses and insurers alike.

Further, some medications are prescribed for multiple symptoms, including epilepsy. The legislation would prohibit substitution of these medications if they are used in the treatment of epilepsy, but not if they are used for other conditions. Patients receiving a generic epilepsy medication may find it difficult to receive treatment when the pharmacy provider selects an alternate generic manufacturer of the product, whether the product is commonly used to treat epilepsy or not.

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Proponents Raise Concerns: Pharmacist Consultations

In the past representatives of the Epilepsy Foundation have publicly stated that some pharmacists do not perform an adequate consultation when dispensing medications to epileptic patients. For instance, the Foundation has asserted that patients are not told when a pharmacy has filled the prescription order with a medication from a different manufacturer when dispensing an A/B generic equivalent. In a memorandum circulated to legislative offices drafted by the authors of the bills and the Epilepsy Foundation they asserted that, "under current law pharmacists may switch a patient's prescription from one epilepsy medication to another without the consent of the doctor who wrote the prescription. Medication substitutions occur haphazardly, without the knowledge or consent of the physician or in some cases even the patient."

This is false; in fact it is illegal for a pharmacist to switch a medication for any patient without the consent of the prescribing practitioner. Furthermore, pharmacists do not haphazardly make any changes; this is simply an inflammatory comment. PSW advocates that pharmacists advise all patients of instances when a manufacturer of a prescription drug used by a patient changes.

Bioequivalence of Substituted Products

The major concerns raised by proponents of this legislation are problems that may arise with the substitution of any medication used in the treatment of epilepsy. They argue that patients who have epilepsy should be allowed to maintain access to the same medication by the same manufacturer in order to minimize the potential of

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a seizure due to therapeutic differences between products. To illustrate this point, advocates reference the bioequivalence of generic medications not only from their brand name counter-parts but also from generic to generic.

The United States Food and Drug Administration states, "a generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance and intended use. The FDA bases evaluations of substitutability or "therapeutic equivalence" of generic drugs by requiring and testing that the drug product must contain identical amounts of the same active ingredient(s) as the brand name product. Drug products evaluated as "therapeutically equivalent" can be expected to have equal effect and no difference when substituted for the brand name product."

Bioequivalence of different versions of a drug can vary by up to 20%, because for most drugs, such variation does not noticeably alter effectiveness or safety. However, actual differences between FDA-approved generic and trade-name drugs are generally much smaller than the allowable 20%. The FDA reports that actual differences are 3.5% on average and rarely exceed 10% in any single study of bioequivalence. PSW recognizes that sometimes generic substitution is not appropriate. For example, some generic versions cannot be determined to be bioequivalent to the original drug because no standards for comparison have been established. These versions should not, and in Wisconsin may not, be interchanged for the original drug.

PSW Recommended Action

PSW recommends that the legislation be rejected. PSW further recommends that the Office of the Insurance Commissioner ensure that patients with epilepsy are not inappropriately denied access to necessary therapies by their insurer or health plan.

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WISCONSIN PHARMACY QUALITY**COLLABORATIVE**
an initiative of the pharmacy society of wisconsin

Executive Summary

Introduction: The Wisconsin Pharmacy Quality Collaborative (WPQC) is an initiative designed to improve the quality and reduce the cost associated with prescription drug use in the state, launched by Wisconsin's leading health care purchasers and pharmacy providers. The collaborating stakeholders have developed a new model for how payors and community-based pharmacies interact in order to optimize the pharmaceutical products and services provided to patients in Wisconsin. The new WPQC model will define, measure and provide incentives for quality in community pharmacy practice, provide a structure for non-product based pharmacy services, and establish the communication links between payors and pharmacies necessary in order to provide medication therapy management services to the persons that need it most.

The WPQC was organized by the Pharmacy Society of Wisconsin (PSW) and consists of representatives from pharmacy practice, public agencies, managed care groups, traditional indemnity health insurers, and the University of Wisconsin.

Common Goals: Payors and community pharmacy share the common goal of improving patient outcomes through the rational, safe and effective use of medications. Elsewhere in the healthcare system there has been a movement to focus on the quality of care, with a variety of programs and organizations designed to measure and improve quality of care. Examples include the National Committee for Quality Assurance (NCQA), the Wisconsin Collaborative for HealthCare Quality (WCHQ), the Leapfrog Group, and the CMS-sponsored national Pharmacy Quality Alliance (PQA). Pharmacists, being located within the community and interacting with patients on a monthly basis, are ideally situated to improve the quality of medication use.

The Current Situation: The current payor to pharmacy reimbursement structure lends itself to limited collaboration and decreasing ability to provide quality services over time. This is due to a variety of factors:

1. A lack of quantitative or qualitative means of measuring quality in community pharmacy practice. Payors cannot differentiate the highest quality pharmacy in their network from the lowest quality pharmacy. Little data is also available for consumers to differentiate pharmacies by the quality of the services they provide.
2. Product-based reimbursement structure. Currently, the medications dispensed and the professional services provided by a pharmacy are covered under the same reimbursement, which is based on the cost of the drug dispensed. Pharmacies utilizing additional resources to provide high quality services are paid the same as those that provide minimal services, because the reimbursement is tied to the drug product dispensed. There is currently a financial disincentive for pharmacy providers to invest resources to ensure high quality and provide targeted medication management services.
3. Competitive pressures amongst payors. Whether it is an employer paying for employee benefits, or a managed care organization administering a drug benefit, competitive pressures faced by payors result in all payors seeking the reimbursement rates set by their lowest reimbursing competitor. When pharmacies accept lower reimbursement contracts from one payor, eventually all payors will be forced to seek similar reimbursement levels to remain competitive. While this market phenomenon may reduce the amount paid for

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prescription drugs, it also forces dispensing efficiency and prescription volume as the major focal points for pharmacy providers—not ensuring optimal medication use.

4. The result of the three marketplace factors outlined above provides no business reason for a pharmacy to invest in providing higher quality services. In fact, the furthering of these market forces over time reduces the probability of a community pharmacist serving as a health care resource.
5. Claims adjudication systems do not serve as patient management systems. In addition to the lack of a business reason for pharmacies to pursue high quality care, there is a limited amount of patient management interaction between payors and community pharmacies. Payors often have a wealth of patient specific information that could steer pharmacist's efforts towards those patients who would benefit most or to those for whom the payor would most value an interaction (based on quality measures and cost). The primary form of interaction between payors and pharmacies is the payor's prescription drug claim adjudication system. Pharmacy claims adjudication systems allow for only very limited information about the patient to be transmitted to the pharmacy and do not allow the payor to identify patients to the pharmacy for specific interventions.
6. Experience is limited. Experience with large scale payor-pharmacy collaborations of this sort is extremely limited. Participating in such a project is new for most payors and pharmacy providers. This uncertainty has often resulted in a climate where payors or pharmacies are unwilling to venture forth without asking the other party to accept the risk of change. As a result, change and a focus on quality improvement has not happened.

To build a new model that emphasizes quality improvement and cost reduction, the WPQC is proposing that a pilot program be carried out with a select number of interested pharmacies and Wisconsin health care purchasers. Although a comprehensive evaluation will be conducted of the WPQC pilot program to measure the improvement in quality and the health care cost savings, evidence suggests that there is a direct correlation between quality and cost. Similar projects have resulted in savings of $4 for every $1 invested.

Return on Investment: Numerous reports have demonstrated the ability of pharmacist services to improve outcomes and provide a positive return on investment.

"Asheville studies"
Diabetes: Total health care costs decreased by an average of $2000/patient/year and patients' missed work hours decreased by 50%.
J Am Pharm Assoc. 2003;43:149–59; J Am Pharm Assoc. 2003;43:173–84
Asthma: Total health care costs decreased by an average of $725/patient/year and patients' missed work hours decreased by 400%.
J Am Pharm Assoc. 2006;46:133–147
ROI: calculated by employers (4:1)

Touchpoint insurance company intervention-based pharmacy reimbursement 1998 unpublished data
ROI: estimated 6:1

Decrease in Preventable Adverse Drug Events
Arch Intern Med. 2006;166:565-571

92/178 patients discharged home from the general medicine service at a large teaching hospital received pharmacist counseling at discharge and a follow-up telephone call 3 to 5 days later. The primary outcome was rate of preventable ADEs. 30 days after discharge,

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preventable ADEs were detected in 11% of patients in the control group and 1% of patients in the intervention group (P=.01). No differences were found between groups in total ADEs or total health care utilization.

Although these reports indicate that the investment in pharmacist services provides a savings that can outweigh the costs, the proposed pilot program is unique in its scope, and it will be difficult to directly apply previous ROI estimates. For this reason, an important goal of the pilot program is to measure the results of the program and better define the return on the investment for all participants.

In the pilot program, participating pharmacies will provide value to patients and payors in several ways. The WPQC has worked to identify and define the value or return on investment for all of the services that may be provided. The following provides a description for each type of service.

Quality-based Pharmacy Network Requirements ROI: Based on the criteria which pharmacies must meet to qualify for participation in the program, all patients receiving prescriptions from participating pharmacies will benefit from the best practices in community pharmacy. Although it is difficult to quantify the dollar value for these activities, the standards represent a significant improvement over the standard of care in most community pharmacies today.

The overall effect on patients of these best practices is:

- Decreased medication errors
- Decreased duplicate therapy
- Decreased under or overdoses
- Increased patient understanding of their medications
- Increased patient satisfaction with their pharmacy

In the long term, these effects will result in fewer adverse drug reactions that may translate into fewer office visits, emergency room visits, hospitalizations or additional prescriptions.

Although we do not have data to indicate specific dollar savings for implementing best practices in this area, a recent Institute of Medicine report entitled "Preventing Medication Errors" outlines the tremendous cost of adverse drug reactions to the health system. As a result of many such reports in the past several years, prevention of medication errors and adverse drug reactions has been pushed to the forefront as a quality focus nationwide.

Additionally, the requirements will result in identification of higher level drug therapy issues or cost savings opportunities that will then be addressed within the Level I (intervention-based) Services aspect of this program.

Level I (Intervention-based) Services ROI: This service level is the most straightforward in terms of identifying return on investment. Although some of the services included do not result in directly quantifiable savings (e.g. medication device instruction intervention), the savings for others can be readily identified. These product-oriented services include cost effectiveness interchange interventions such as formulary interchanges and tablet splitting. Based on the experience of Wisconsin health plans already reimbursing for similar services, the savings associated with product oriented services pay for the quality oriented services and still result in an overall savings. The balance results in about a 6:1 return on investment.

The ability to steer utilization to the most cost effective options through the cost effectiveness intervention provides an additional utilization management tool to payors to maximize the utilization of the most cost effective options within a drug class.

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Additional value is provided for payors with services that directly assist in improvement of patient outcomes and HEDIS measures such as focused adherence interventions, medication device instruction interventions and medication additions or deletions interventions based upon adherence to clinical guidelines. Payors can incorporate these services into their existing disease management programs.

Level II (Comprehensive Medication Review and Assessment) Services ROI: Comprehensive Medication Review and Assessment (CMR/A) is focused on high risk patients. For most payors, a small percentage of covered patients drive the majority of costs. CMR/A Services will allow payors to direct individual pharmaceutical care to the specific patients who need it the most.

CMS saw the value of such services when defining the requirements of prescription drug plans participating in the Medicare Part D benefit. The CMR/A is loosely modeled after the Medication Therapy Management (MTM) requirement of Medicare prescription drug plans. While many models of utilizing pharmacists to provide comprehensive drug therapy management services have shown benefits as noted earlier in the document, the results are not yet in with the Medicare MTM programs.

CMR/A will result in:

- Optimization of patients' medication regimens
- Better patient understanding of their medications and the importance of each
- Improved medication adherence
- Fewer adverse drug reactions
- Improved attainment of clinical goals /outcomes

The impact of these benefits may result in increased or decreased pharmacy costs to the payors, but it is hoped that the true benefit will be seen in improved medical outcomes and a resulting decrease in associated medical costs.

As with the other aspects of this program, the WPQC has made a high priority of studying the results of CMR/A and identifying ROI.

Additional Value: The program as a whole will provide value to payors in a few additional areas:

- For the first time, payors will be able to differentiate pharmacies in their network based on quality.
- Payors already providing reimbursement for some of the services will see an increase in participation due to standardization and increased opportunities for pharmacies.
- Payors participating in the project will be recognized in an aggressive publicity campaign for the project. Participants will be seen as innovative leaders.

Conclusion: The Wisconsin Pharmacy Quality Collaborative represents an innovative model to reverse some of the issues preventing community pharmacy and payors from realizing the potential of working together. Since the WPQC pilot project is so unique and ground breaking, we do not have hard and fast dollar savings or return on investment numbers from which payors and pharmacies may make a business decision of whether to participate. However, the reluctance to pursue quality due to the unknown quantity of return on investment is one of the primary reasons we have made only limited progress with this type of collaboration in the past. For Wisconsin residents to realize the benefits of payors and pharmacies working together to improve their health, both parties need to step forward at the same time.

Assembly Bill 506 (AB506) and Senate Bill (SB354)
Creating new barriers to care of epileptic patients?

AB506 and SB354 have been proposed to ensure that patients being treated for epilepsy receive an identical pharmaceutical product each time a prescription is refilled. The proposed legislation is brought forth by its sponsors with good intentions; namely, that patients whose epilepsy is so fragile that any medication change, even between therapeutically equivalent products, could theoretically result in a breakthrough seizure and its consequences. Current state laws allow for such desired consistency through the use of the "Dispense As Written", or DAW notation on each prescription. Physicians also use "Do Not Substitute" on prescriptions, which is the same as DAW. The proposed legislation would achieve its desired intent only if all of the following conditions were true:

1. Each patient uses the same pharmacy to fill and refill each prescription.
Different pharmacies use different wholesalers and have access to different generic products through those wholesalers. Pharmacies do not have visibility to the dispensed products from other pharmacies. Patients would need to know what generic product was last dispensed, and what pharmacies stock this product, a daunting challenge for even the most knowledgeable patient.

2. Each patient receives prescriptions from only one physician.
Physicians are often difficult to reach in the event of a supply issue. If the pharmacy does not have the desired medication in stock, it may take several days to contact the original prescriber to authorize a change or refill. It would be far more likely that an on call physician would issue a NEW prescription to ensure an uninterrupted supply of medication. At this point a different generic could be introduced. The original physician would not know what the patient had been switched to and when the original physician refilled the prescription again may request the first generic, resulting in another medication switch. This system could potentially result in more medication changes for a patient than appropriate use of the current state law's DAW provision.

3. Each patient anticipates the need for a prescription refill well in advance of running out of medications to allow the pharmacy time to obtain the same generic.
As much as we would like our patients to be on top of their medication supplies, 80-85% of patients using Dean Pharmacies request refills AFTER THEY HAVE TAKEN THEIR LAST PILL, and this tends to happen in the evening and on weekends when access to physicians is limited. In this situation an on-call physician is likely to issue a NEW prescription to accommodate pharmacy filling at a pharmacy with expanded hours, again introducing a medication change with no visibility by the patient's usual dispensing pharmacy or by the usual prescribing physician. New prescriptions do not state which specific drug product to use, it is the pharmacy's choice.

4. Each pharmacy is able to maintain a consistent stock of the desired product, at all times.

In the ideal world, all pharmacies would stock all possible variations of a generic medication. In reality this never happens, pharmacies stock products according to wholesaler availability and price. Wholesalers will substitute therapeutically equivalent products on orders when the desired product is out of stock. Wholesalers also constantly re-negotiate contracts to obtain the best pricing and what a pharmacy is able to purchase on contract one month may be different the next month.

5. Each physician is accessible for authorization of a prescription should a question arise.

Physicians should concentrate their efforts on patient care and minimize interruptions. To that end, it is very difficult to directly contact a prescriber. In the event of a product being out of stock, obtaining the same product will require the patient to either call around to all area pharmacies to find out who carries the desired generic or wait until the physician can be contacted, which may take several days. For patients in rural areas, patients may have access to only one pharmacy, and may have to wait several days for that pharmacy to obtain the desired drug. The proposed legislation ties the hands of the pharmacist who is able to supply an equivalent generic until a physician can be contacted to authorize dispensing a different product which will mean that patients will go without medication. Is it better to skip medication than to make a therapeutic substitution? Absolutely not.

6. Physician electronic medical records systems have the capacity to discern one generically equivalent product from another.

The Epic system, used extensively by health systems in the Madison area, has NO capacity to track generic equivalents to the product level. The DAW capability is built into the system; passage of the proposed legislation would require an expensive rebuild of the medication ordering module in the Epic system and may not even be technically possible. Physicians would have no common visibility to the products dispensed once a prescription has been sent electronically until such reprogramming could happen, if ever.

7. All patients have insurance plans that impose no monetary penalties when a brand is mandated or when a specific generic is required.

Again, this is basically never true. In the proposed legislation, the physician involved in a hospitalized patient's care may prescribe a brand only product because that is what the hospital stocks and at discharge the patient would have no option to "opt out" of a branded drug because the patient doesn't want to pay a brand copay and would have to wait to receive their medication until a physician could sign off on a generic alternative. As an example, some patients with certain Dean Health employer-sponsored insurance plans pay a co-insurance for brand medications, not a co-pay. This is not uncommon for other insurance plans throughout the state. Patients who are prescribed a medication subject to co-insurance may be liable for 20-30% of the retail cost of a medication. Instead of paying a generic copay of $5, a patient receiving branded Lamictal instead of generic lamotrigine could pay as much

as $95 for the branded product and the dispensing pharmacy would be prohibited from dispensing the generic alternative even if requested by the patient, until the physician could be contacted.

In the real world, none of these conditions are true at all times, and some of them are never true. Introducing the need for physician authorization for refills introduces the very real potential that patients who are out of their medication will not be able to have their prescription filled until their prescriber can be contacted and authorize a substitution if the previously dispensed product is not available. If a patient goes without doses of antiepileptic medication while waiting, the theoretical risk of a breakthrough seizure becomes a very real risk. The proposed legislation attempts to provide a theoretical benefit to a few fragile patients while it introduces a real risk of interruptions in therapy to many patients who are well-maintained on available generic equivalents.

Submitted by Mary Swandby, RPh
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October 22, 2009

Generic Substitution of Anti-Epileptic Medications:

A Clinical, Safety and Scientific Perspective

Howard Rutman, MD
Group Vice President
Medical Director
Taro Pharmaceuticals USA

State of Wisconsin
Assembly Public Health Committee
Senate Health, Health Insurance, Privacy, Property Tax Relief and Revenue
October 22, 2009

Why am I here?

- Practicing physician
  - 22 years in clinical and academic practice
  - Board Certified in Internal Medicine and Cardiology
- Medical Director for Taro Pharmaceuticals
  - Oversee global Drug Safety
    - US, Canada, UK and Israel
  - Products include anti-epileptics
    - Carbamazepine, lamotrigine, levetiracetam, phenytoin
- Work with the Generic Pharmaceutical Association

Clinical Perspective

- Our goal is to make sure that patients receive the safe and effective medications that they need
- This is true for all medical conditions, and especially true for patients with chronic, serious medical conditions such as epilepsy

Treatments Must be Individualized

- The vast majority of patients with seizures will respond to a broad range of anti-epileptic medications
- Dosages should be monitored – but, most patients will achieve adequate control on a stable medical regimen with little variability in drug levels or therapeutic response

Special Needs

- Occasionally patients with epilepsy have complex medical regimens and require particular attention to formulations and methods of administration
- Physicians already can specify the Reference Listed "Brand Name" product by indicating "***No substitution***"

Accessibility Matters

- **No medication works unless it is taken**
- Patients with limited financial means often fail to fill prescriptions or miss doses because of the cost
- This is a recipe for disaster in patients with seizures
- Safe, effective and affordable medications are need for epilepsy patients

Safe – Effective – Affordable

- What does the FDA do to establish bioequivalence?
- What is the safety track record of generic medications for patients with epilepsy?
- What prospective, scientifically valid information is available?

FDA evaluates generics fully during the approval process

- The FDA evaluates the entire manufacturing process
  - Includes source of active pharmaceutical ingredient
  - All inactive ingredients meet USP standards
  - Manufacturing and testing controls are validated
  - Dissolution and stability testing must be the same as the brand
- FDA can mandate additional in process and release standards to make sure that the products are bioequivalent

FDA can evaluate the full record in bioequivalence studies

- FDA has access to the full record for each individual patient in bioequivalence studies
- The FDA can identify outlier patients or site to site variability
- Bioequivalence required by FDA is more sophisticated than just the average pharmacokinetic response
  - It takes into account patient to patient variability
  - The response of individual patients must be similar in order to pass bioequivalence testing

FDA Description of Bioequivalence Requirements

- **Steven K. Galson, M.D. – 2004**
  - Acting Director FDA Center for Drug Evaluation and Research
- "It *(the -20/--25% "rule")* actually represents acceptable bounds on the 90% confidence intervals around the ratio of the mean results for each of the two products. In practice, because of human variability, this means that the actual results for rate and extent have to be very close. FDA did a study in the 1980's evaluating 224 bioequivalence studies that "passed" the -20/+25 rule. In these studies, the average observed difference in absorption between the brand name and the generic was about 3.5%. It is important to note that FDA applies an identical bioequivalence standard to brand name products when significant changes in manufacturing or formulation occur. Nevertheless, the degree of regulatory control over rate and extent of absorption for any formulation is the same for a generic and branded drug."

FDA monitors generic manufacturers just like the brands

- FDA routinely inspects generic manufacturing facility – must meet current Good Manufacturing Procedures
- Generic manufacturers submit annual reports on manufacturing processes and stability
- FDA is aware of manufacturing or stability issues
  - Branded companies may have the same or even more batch to batch variability than some generics
- *Only the FDA sees the full record for ALL manufacturers*

FDA can best assess safety risks

- Both generic and branded manufacturers submit Adverse Event reports to the FDA
- FDA receives all the adverse event reports and can compare across various products
- *Only the FDA is in a position to know whether there is a safety issue related to a particular branded or generic formulation of a product*

Example: Carbamazepine

- Long established anti-epileptic – brand name Tegretol®
- Generic versions have been available to patients for many years
- Generic medications are widely used
- Clinical studies support safety and efficacy of generic carbamazepine

Generic Carbamazepine Long Track Record

- Generic Carbamazepine products have been on the market for >20 years
- They have been used by millions of epileptic patients
- Excellent safety record

First Carbamazepine Approval	
Manufacturer	Year
Teva	1986
Actavis	1987
Taro	1996
Caraco	2001
Apotex	2002
Morton Grove	2002

Carbamazepine market

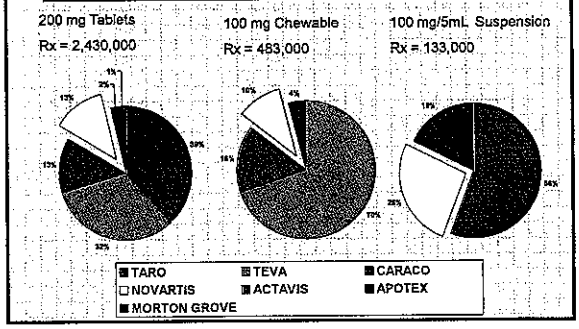
- Immediate release tablets, chewable tablets and suspension
  - Total US annual Rx's: 3.05 Million
  - Physicians cans choose Brand or Generic
- Extended release tablets and capsules
  - Total US annual Rx's: 1.88 Million
  - Available as brand products only

All Sales Data from Wolters Kluwer© - data through November 2007

Generic Medications: Widely Accepted

- For all formulations for which generic products exist, the generic product outsells the branded products
  - Immediate release tablets
  - Chewable tablets
  - Suspension
- Brand name product from Novartis is not the market leader in any of these forms

Carbamazepine formulations



Published data on generic carbamazepine

- Prospective, randomized, controlled trials
- Multi-dose pharmacokinetic studies
- Clinical cross-over studies

Multiple dose pharmacokinetics

A multiple-dose safety and bioequivalence study of a narrow therapeutic index drug: A case for carbamazepine

Avraham Yacobi, PhD, Steve Zlotnick, PharmD, RPh, John L. Colaizzi, PhD, Daniel Moros, MD, Eric Masson, PharmD, Zohreh Abolfathi, PhD, Marc LeBel, PharmD, Rakesh Mehta, PhD, Yechiel Golander, PhD, and Barrie Levitt, MD
Hawthorne, New York, and Bronx, NY; East Brunswick, NJ, and Sainte-Foy, Quebec, Canada

CLINICAL PHARMACOLOGY & THERAPEUTICS
APRIL 1999

Study conducted by Taro along with Rutgers University and Anapharm

Study design

- Compared an FDA approved generic formulation to the branded product
- Subjects (n=28) received generic product for 7 days compared to branded product for 7 days

Brand and Generic Products Are Very Similar

	Generic	Brand
% Average Tablet Content	101	98.6
Content Uniformity		
% Average Tablet Content	100	100
% Lowest Assay Value	99.0	95.6
% Highest Assay Value	102	103
%RSD	1.1	2.2

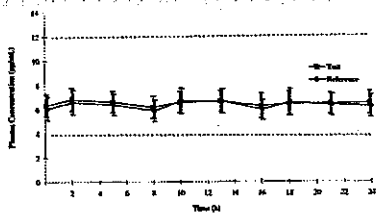
- Generic has slightly ***lower*** variability than Brand

Steady State Cross-Over Results

	Mean values (CV%)				
Parameter	Generic	Brand	Ratio	p-Value	90% CI
AUC (µg-h/mL)	156 (13.2)	153 (13.7)	1.02	NS	100-104
Cmax (µg/mL)	7.11 (12.9)	7.10 (12.9)	1.0	NS	98-103
Cmin (µg/mL)	5.90 (15.1)	5.65 (14.8)	1.04	T>R	102-107
Cavg (µg/mL)	6.52 (13.2)	6.39 (13.7)	1.02	NS	100-104
tmax (h)	11.6 (76.3)	12.6 (52.8)	0.92	NS	
Fluctuation %	18.8 (51.8)	23.0 (31.9)	0.82	T<R	

- All metabolic parameters are within 4% of each other
- Fluctuation was slightly greater with Brand

Steady State Profile



- Blood levels are very stable over time
- No difference between Brand and Generic

Conclusions from multi-dose pharmacokinetic study

- No difference in metabolic parameters between Brand and Generic
- Levels of carbamazepine and its metabolite are very stable at steady state
  - Less than 5% variability
- FDA criteria of bioequivalence confirmed in multi-dose study

US cross-over study in patients with epilepsy

- Randomized, double-blind, cross-over study in 40 epileptic patients taking carbamazepine for 6 or more months
  - 13 to 70 yeas-old
- Received 90-day courses of treatment with Brand and Generic
  - Order determined at random

Oles KS, Penry JK, Smith LD, Anderson RL, Dean JC, Riela AR. Therapeutic bioequivalency study of brand name versus generic carbamazepine.Neurology. 1992 Jun;42(6):1147-53.

Clinical Patient Types

- Looked at a wide variety of patient types
- Included patients who were "well-controlled" on carbamazepine alone
- Also included patients who were on carbamazepine along with other medications and still having seizures

Blood level results

- No difference in blood level concentrations between Brand and Generic
  - Difference < 5%
- No difference in Fluctuation Index over 3 month treatment period

Conclusion from US cross-over study in patients with epilepsy

- Patient outcomes were the same on Brand and Generic
- No difference in overall seizure frequency between Brand and Generic
- No difference in breakthrough seizures in "controlled patients"
- Breakthrough seizures were NOT related to changes in blood level between products
- No difference in side-effects

International Studies

- European Study compared Novartis Tegretol to 2 European generic products
- Found no difference in blood levels between the products
- All products equally well tolerated
- No difference in side effects

Aldenkamp AP, Rentmeester T, Hulsman J, Majoie M, Doelman J, Diepman L, Schellekens A, Franken M, Olling M. Pharmacokinetics and cognitive effects of carbamazepine formulations with different dissolution rates. Eur J Clin Pharmacol. 1998 Apr;54(2):185-92.

International Studies

- Asian study compared Novartis Tegretol to 3 generic products
- 18 patients with epilepsy treated for 3 weeks with each product
  - Age range 15-49
  - Dose 400-1000 mg (average 677 mg/day)
  - Concomitant medications – valproate, clonazepam, phenobarbital, haloperidol, thioridazine

Silpakit O, Amornpichetkoon M, Kaojarern S. Comparative study of bioavailability and clinical efficacy of carbamazepine in epileptic patients. Ann Pharmacother. 1997 May;31(5):548-52.

Results

	No Seizures	Breakthrough Patients	Total Seizures
Generic 1	16/18	2/18	5
Generic 2	11/18	7/18	14
Generic 3	15/18	3/18	5
Brand	13/18	5/18	10

- No difference in seizure frequency related to Brand or Generic
- No difference in side-effects
- No difference in patient outcomes

Conclusions from randomized prospective, controlled studies

- Multi-dose cross-over demonstrates metabolic equivalence between Brand and Generic
- No difference in breakthrough seizures or seizure frequency
- No difference side-effects
- Patients do well on generic anti-epileptic medications

Clinical Trial Data Support Generic Substitution

- Harvard Systematic Review and Meta-Analysis
  - Looked at 47 studies in cardiovascular therapeutics
  - Included "narrow therapeutic index (NTI)" medications – warfarin and antiarrhythmics
- "The studies in our sample concluded that generic and brand-name cardiovascular drugs are similar in nearly all clinical outcomes."
- "Our results suggest that it is reasonable for physicians and patients to rely on FDA bioequivalence rating as a proxy for clinical equivalence among a number of important cardiovascular drugs, even in higher-risk contexts such as the NTI drug warfarin."

Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK, Shrank WH. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA*. 2008 Dec 3;300(21):2514-26.

Meeting Patients' Needs

- Occasional individual patients might need a branded or specific formulation product
- ***"No substitution" provides the mechanism for those situations***
- For most patients *access* to medications is critical
- Generics provide a safe and effective alternative

Meeting Patients' Needs

- The FDA has the most complete data on the safety and equivalence of generic products
- The FDA process can be relied on to demonstrate that brand and generic products are equivalent
- The published scientific data supports the safety, efficacy and interchangeability of generic products

Carbamazepine Safety

- Important safety information below
- Please see full prescribing information before prescribing this product

Carbamazepine
Brand Name: Tegretol®

- **INDICATIONS AND USAGE**
- **Epilepsy:** Carbamazepine is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:
  - Partial seizures with complex symptomatology
  - Generalized tonic-clonic seizures (grand mal).
  - Mixed seizure patterns which include the above, or other partial or generalized seizures.
- **Trigeminal Neuralgia**

Black Box Warnings

WARNING
SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE
SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY ATRISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBAMAZEPINE UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS** AND **PRECAUTIONS/LABORATORY TESTS**).

Black Box Warnings

APLASTIC ANEMIA AND AGRANULOCYTOSIS
APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE CONTROLSTUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

- New HLA data – added December, 2007
- These Adverse Events are NOT dose or formulation related
- Generics and Brand carry identical labeling

Contraindications

CONTRAINDICATIONS
Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

Adverse Reactions

The most severe adverse reactions have been observed in the hemopoietic system (see boxed ***WARNING***), the skin, and the cardiovascular system.
Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.
Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see ***WARNINGS***), Stevens-Johnson syndrome (see ***WARNINGS***), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.
Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.

Adverse Reactions

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

- More common adverse reactions may be dose related
- Most serious adverse reactions are not dose related

NACDS NATIONAL ASSOCIATION OF CHAIN DRUG STORES

TESTIMONY IN OPPOSITION TO ASSEMBLY BILL 506 AND SENATE BILL 354

BY

DALE MASTEN, NACDS

OCTOBER 22, 2009

413 North Lee Street
P.O. Box 1417-D49
Alexandria, Virginia
22313-1480

Good Afternoon, Chairmen and Members of the Committees, my name is Dale Masten, I am the Director of State Government Affairs for the National Association of Chain Drug Stores (NACDS). On behalf of the approximately 545 chain pharmacies operating in the state of Wisconsin, I would like to thank the Committee on Health, Health Insurance, Privacy, Property Tax Relief, and Revenue and the Committee on Public Health for considering our concerns with Assembly Bill 506 and Senate Bill 354 which would establish special requirements for generic substitution of epilepsy drugs. NACDS members believe that theses bills would create duplicative and unnecessary requirements that would serve only to discourage the use of cost saving generic drugs. We respectfully ask you to consider our comments about why this type of legislation is unwarranted, and vote not to pass the legislation out of committee.

Legislation that would create a special requirement for epilepsy drugs is unnecessary because Wisconsin law already provides a well-established means for a prescriber to instruct a pharmacist to dispense a brand name drug. In accordance with the requirements of W.S.A. 450.13, a pharmacist must dispense "the specific drug product prescribed" when the prescriber designates on the prescription "no substitutions" or words of similar meaning to indicate that substitution is not allowed. The prescriber makes the decision as to whether or not generic substitution is appropriate for a particular patient at the time when the prescription is issued. There is no benefit or improvement in care achieved by requiring a pharmacist to obtain additional consent; when the physician

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has in effect, already given consent by not employing his or her statutory ability to prevent a substitution. Verifying the ability to substitute unnecessarily reconfirms the prescriber's earlier decision. Furthermore, the record generated by documenting this act would essentially be a duplicate of the consent already given via the original prescription. Additional, special requirements on top of the current law serve no purpose other than to discourage pharmacists from providing cost saving, equally effective generic drugs to patients and to create fear in patients who are or could be well-controlled on a generic drug.

Through its rigorous approval process, the FDA requires generic drugs to have the same quality and performance as their brand name drug counterparts. FDA only approves generic versions of brand drugs when the generic has the same active ingredient, strength, dosage form, and route of administration and meets the agency's criteria for bioequivalency. Approved generic products are assigned a "rating" in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations", commonly called the FDA "Orange Book"; any product listed in the "Orange Book" as having the same active ingredients, strength, dosage form and route of administration, which has been given an "AB rating," can be safely substituted for another product with the same AB rating. ***This applies both to the substitution of a generic for a brand and to the substitution of one generic for another generic.*** FDA applies this strict standard to all classes of drugs, including drugs used to treat epilepsy.

According to the FDA Office of Generic Drugs, "[t]he American public can be confident that when a generic drug product is approved, it has met the rigorous standards established by the FDA with respect to identity, strength, quality, purity and potency. Through review of data on proposed products, the Office of Generic Drugs assures that generic product will perform the same as their respective brand name reference products. In the same manner, generic manufacturing and packaging sites must pass all of the same quality standards as those of brand name drugs and the generic products must meet the same exacting specifications as any new innovator drug product."[1]

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[1] http://www.fda.gov/cder/ogd/welcome_to_ogd.htm

FDA has also specifically addressed concerns regarding the therapeutic equivalence of drugs prescribed for epilepsy patients. In a 2008 letter from FDA, the Agency advises that they are "aware that certain individuals and groups have expressed particular concern about the switching of epilepsy drug products," and indicates that they have seen "no scientific evidence that demonstrates a particular problem with this group of products."[2] In fact, there are "frequently circumstances other than the switch that may cause untoward response." Furthermore, FDA's letter notes that their position continues to be that health care providers need not approach any one therapeutic class of drug products differently from any other class when there has been a determination of therapeutic equivalence by FDA.

Assembly Bill 506 and Senate Bill 354 would create onerous logistical challenges for pharmacists to serve their patients. Obtaining special consents to dispense generic drugs could force pharmacists to fill prescriptions with more expensive brand name products in order to provide the patient timely and efficient access to their medications, even if the patient prefers to receive the generically equivalent product. The unfortunate result of this untenable scenario is that patients may have no choice other than to pay higher prices for the more expensive brand product via copays, other cost-sharing, or the full cost of the drug. Therefore patients, employers, insurance companies, and state insurance plans would have no choice other than to pay higher prices for the more expensive brand product. Particularly in these trying economic times, it would be imprudent to pass legislation that would so drastically increase healthcare costs. One potential impact is the cost to Wisconsin's Medicaid Department. If you limit the number of generics in any prescription drug program, the cost to the program will increase. This seems detrimental to the direction in which Medicaid was trying to go when implementing their reform package. With the State estimating a 6.6 billion deficit dollar deficit in the 2009-2011 fiscal year, and Medicaid trying to save 600 million dollars, this legislation goes in the opposite direction.

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[2] Gary Buehler, R.Ph., Director, Office of Generic Drugs, FDA; Letter to the Iowa Pharmacy Association; 11 January 2008.

Another detrimental impact is the number of drugs that will be affected. The bill defines the impacted drugs as "a drug prescribed for the treatment of epilepsy or a drug used to treat or prevent seizures." There are many prescriptions issued for "off-label" use meaning, the drug, while may be used to treat seizures, it may also be used to treat other conditions. For example, Neurontin is a drug used to treat epilepsy; however, it is prescribed to alleviate leg pain in people with diabetes, or shingles pain. Also, the popular anti-anxiety drug Valium is used to treat epilepsy. Both of these drugs, and many more would require the pharmacist to obtain the proper consent when substituting for a generic. This would affect patients who do not have epilepsy.

Again, NACDS appreciates the opportunity to testify in opposition to these bills. We ask that you vote not to pass Assembly Bill 506 and Senate Bill 354 out of committee, and thus not establish special requirements for the generic substitution of epilepsy drugs. Thank you and I will be happy to try and answer any questions.

U.S. Food and Drug Administration

Facts and Myths about Generic Drugs

Today, 7 in 10 prescriptions filled in the United States are for generic drugs. This fact sheet explains how generic drugs are made and approved and debunks some common myths about these products.

FACT: FDA requires generic drugs to have the same quality and performance as the brand name drugs.

- When a generic drug product is approved, it has met rigorous standards established by the FDA with respect to identity, strength, quality, purity and potency. Some variability can and does occur during manufacturing, for both brand name and generic drugs. When a drug, generic or brand name, is mass produced, very small variations in purity, size, strength and other parameters are permitted. FDA puts limits on how much variability in composition or performance of a drug is acceptable.
- Generic drugs are required to have the same active ingredient, strength, dosage form, and route of administration as the brand name (or reference) product. Generic drugs do not need to contain the same inactive ingredients as the brand product.
- Through review of bioequivalence data, FDA assures that the generic product will perform the same as its respective brand name (or reference) product. This standard applies to all generic drugs, whether immediate or controlled release.
- A generic drug must be shown to be bioequivalent to the reference drug; that is, it must be shown to give blood levels that are very similar to those of the reference product. If blood levels are the same, the therapeutic effect will be the same. In that case, there is no need to carry out a clinical effectiveness study and they are not required.
- All generic manufacturing, packaging and testing sites must pass the same quality standards as those of brand name drugs and the generic products must meet the same exacting specifications as any innovator brand name product. In fact, many generic drugs are made in the same plants as innovator brand name drug products.
- If an innovator of a brand name drug switches drug production to an alternative manufacturing site, or they change formulation of their brand name drug, these companies are held to the same rigorous manufacturing requirements as those that apply to generic drug companies.

FACT: Research shows that generics work just as well as brand name drugs.

- A recent study evaluated the results of 38 published clinical trials that compared cardiovascular generic drugs to their brand-name counterparts. There was no evidence that brand-name heart drugs worked any better than generic heart drugs. [Kesselheim et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA. 2008;300(21)2514-2526].

Source: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/Understanding

FACT: When it comes to price, there is a big difference between generic and brand name drugs. On average, the cost of a generic drug is 80 to 85% lower than the brand name product.

- An IMS National Prescription Audit shows that a typical formulary now charges $6 for generic medications, $29 for preferred branded drugs, and $40 or more for non-preferred branded drugs. [Aitken et al. Prescription drug spending trends in the United States: looking beyond the turning point. Health Aff (Millwood). 2009;28(1):w151-60].

- Independent research has shown that total prescription drug expenditures in the United States only increased by 4.0% from 2006 to 2007, with total spending rising from $276 billion to $287 billion. This is a sharp decrease from the 8.9% growth rate observed in prescription drug expenditures in 2006. One factor cited as a reason for the slowdown is an increase in availability and use of generic drugs [Hoffman et al. Projecting future drug expenditures--2009. Am J Health Syst Pharm. 2009;66(3):237-57].

Recently, some misinformation has raised concerns over generic drugs. Below are some common myths in circulation.

MYTH: FDA lets generic drugs differ from the brand name counterpart by up to 45 percent.

FACT: This claim is false. Anyone who repeats this myth does not understand how FDA reviews and approves generic drugs.

- FDA recently evaluated 2,070 human studies conducted between 1996 and 2007. These studies compared the absorption of brand name and generic drugs into a person's body. These studies were submitted to FDA to support approval of generics. The average difference in absorption into the body between the generic and the brand name was **only 3.5 percent** [Davit et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. Ann Pharmacother. 2009;43(10):1583-97]. Some generics were absorbed slightly more, some slightly less. This amount of difference would be expected and acceptable, whether for one batch of brand name drug tested against another batch of the same brand, or for a generic tested against a brand name. In fact, there have been studies in which branded drugs were compared with themselves as well as with a generic. As a rule, the difference for the generic-to-brand comparison was about the same as the brand-to-brand comparison.

- Any generic drug modeled after a single, brand name drug (the reference) must perform approximately the same in the body as the brand name drug. There will always be a slight, but not medically important, level of natural variability – just as there is for one batch of brand name drug to the next.

MYTH: People who are switched to a generic drug are risking treatment failure.

FACT: There is no evidence for this claim. Treatment failures can and do occur when taking generic or brand name drugs. If someone is switched to a generic drug around the time they are relapsing, they may attribute the problem to the switch.

Source: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/Understanding

- Many people who have recovered from major depression have a relapse despite continued treatment. These relapses have been shown in trials of long-term therapy. [Byrne and Rothschild. Loss of antidepressant efficacy during maintenance therapy: possible mechanisms and treatments. J Clin Psychiatry. 1998;59(6):279-88].

- Many people who are on a seizure medications will re-experience a seizure despite continued treatment. [Randomised study of antiepileptic drug withdrawal in patients in remission. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Lancet. 1991;337(8751):1175-80].

- A percentage of people will re-experience gastric ulcers, despite an initial, positive response to and continued treatment with prescription strength antacids (cimetidine tablets; http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8131#nlm34067-9).

MYTH: Generic drugs cost less because they are inferior to brand name drugs.

FACT: Generic manufacturers are able to sell their products for lower prices, not because the products are of lesser quality, but because generic manufacturers generally do not engage in costly advertising, marketing and promotion, or significant research and development.

- When a brand name drug comes off patent and generic drugs are permitted to compete with the brand name drug, the generic products compete by offering lower prices. Unlike the manufacturers of brand name drugs, generic drug companies do not have significant expenses to recoup for advertising, marketing and promotion, or research and development activities.

MYTH: There are quality problems with generic drug manufacturing. A recent recall of generic digoxin (called Digitek) shows that generic drugs put patients at risk.

FACT: FDA's aggressive action in this case demonstrates the high standards to which all prescription drugs – generic and brand name – are held.

- In March 2008, FDA performed a scheduled inspection of the Actavis production facility and identified products that were not manufactured to required specifications over a period of time extending back to the year 2006. Included in this list of products was one particular lot of Digitek.

- Actavis detected a very small number of oversized tablets in this lot (specifically, 20 double-sized tablets in a sample of approximately 4.8 million tablets).

- Although Actavis attempted to remove the affected Digitek tablets through visual inspection, FDA determined that this method of removal was inadequate to assure the product's quality and consistency in accordance with the current Good Manufacturing Practice (cGMP) regulations.

- Since the detection of the manufacturing problem, FDA has been actively engaged with this company to ensure that **ALL** potentially affected lots of Digitek tablets have been recalled. In our best judgment, given the very small number of defective tablets that may

have reached the market and the lack of reported adverse events before the recall, harm to patients was very unlikely.

- FDA takes action whenever we find that a drug manufacturer is not following cGMPs. Over the last ten years, FDA has taken enforcement action against many brand name and generic firms for failing to meet FDA manufacturing quality standards.

MYTH: FDA's enforcement action against the generic drug company Ranbaxy demonstrates quality problems with imported generic drugs.

FACT: FDA's action demonstrates FDA's commitment to safe generic drugs.

- FDA has taken several regulatory actions against the generic drug manufacturer Ranbaxy, on the basis of problems at two of Ranbaxy's manufacturing facilities. Ranbaxy is one of many non-U.S. based generic and brand drug manufacturers.

- On Sept. 2008, the FDA issued two warning letters and instituted an Import Alert barring the entry of all finished drug products and active pharmaceutical ingredients from Ranbaxy's Dewas, Paonta Sahib and Batamandi Unit facilities due to violations of U.S. cGMP requirements. That action barred the commercial importation of 30 different generic drugs into the United States and remains in effect today (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149532.htm).

- Subsequent FDA investigations also revealed a pattern of questionable data raising significant questions regarding the reliability of certain generic drug applications from Ranbaxy.

- To address the allegedly falsified data, the FDA has invoked its Application Integrity Policy (AIP) against the Paonta Sahib facility. When the AIP is implemented, the FDA stops all substantive scientific review of any new or pending drug approval applications that contain data generated by the Paonta Sahib facility. This AIP covers applications that rely on data generated by the Paonta Sahib facility only.

- In the fiscal year 2008, FDA performed 2,221 drug-related inspections. FDA takes many different enforcement actions, not just against generic drug manufacturers. For a list of enforcement actions in the fiscal year 2008, see http://www.fda.gov/downloads/ICECI/EnforcementActions/EnforcementStory/UCM129812.pdf. It is FDA's responsibility to ensure that the drugs people use, generic or brand name, are safe and effective.

MYTH: Brand name drugs are safer than generic drugs.

FACT: FDA receives very few reports of adverse events about specific generic drugs. Most reports of adverse events are related to side effects of the drug ingredient itself.

- The monitoring of postmarket adverse events for all drug products, including generic drugs, is one aspect of the overall FDA effort to evaluate the safety of drugs after approval. In most cases, reports of adverse events generally describe a **known reaction** to the active drug ingredient.

Source: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/Understanding

MYTH: FDA does not care about concerns over generic drugs.

FACT: FDA is actively engaged in making all regulated products – including generic drugs – safer.

- We are aware that there are reports noting that some people may experience an undesired effect when switching from brand name drug to a generic formulation or from one generic drug to another generic drug. Evidence indicates that if problems with interchangeability of drug formulations occur, they occur only for a very small subset of people.
- FDA is encouraging the generic industry to investigate whether, and under what circumstances, such problems occur. The Agency does not have the resources to perform independent clinical studies, and lacks the regulatory authority to require industry to conduct such studies. FDA will continue to investigate these reports to ensure that it has all the facts about these treatment failures and will make recommendations to healthcare professionals and the public if the need arises.

Source: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/Understanding

October 17, 2009

Assembly Committee on Public Health
Room 228 NW
State Capital
Madison, WI

Dear Committee Members:

As the parents of a 22-year-old daughter who suffers from uncontrolled epilepsy and a mild cognitive disability, we continually hope and pray our daughter's seizures will someday be completely controlled. Over the past 16 years since her diagnosis, her seizures have significantly changed in nature and through medical advances reduced from over 20 per day to a few times per month. Her quality of life has thus greatly improved drastically and she is currently employed part time as a sales associate at the New Berlin Goodwill store.

Currently our daughter takes over 20 pills every day at five regulated time periods. We take every possible precautionary measure to safeguard she doesn't miss any of her scheduled medications. We have posted medication schedules, reminder alarms set on her watch, cell phone and pill box, and family members check to ensure her pillboxes are correctly filled and are always taken on schedule. We see our daughter at social events staring at her wristwatch with diligence to ensure she take her pills exactly on time.

One area of grave concern for Katie's welfare is that we can't control errors that can occur in dispersing her prescription medications. When she was a small child, a serious error occurred when an elderly pharmacist admittedly misunderstood her prescription dosage over the telephone. We immediately changed pharmacies. Years later another error occurred when as an inpatient at Children's Hospital, her medical records were misplaced and she was given a reduced level of her prescriptions causing her to experience clusters of grand mal seizures. Most recently, another serious error occurred regarding a vacation refill of her gastric reflux medication this past August 2009. That prescription had just become available in generic form and was substituted in capsules which were double her previous dosages without alerting us or the prescribing physician. The prescribing doctor was overseas visiting family for an entire month. So instead of taking her two 20 mg pills twice a day, she mistakenly took two 40 mg pills twice a day thereby increasing the daily dosage by 4 times the prescribed amount. This mistake occurred consistently for two weeks before it was detected.

As past advocates speaking before this committee for passage of this bill for the past 2 1/2 years, we've learned to always open all our prescription bottles and visually check for any noticeable changes in the medications. In this case, we alerted the pharmacist the capsules were a different color although the same size. The pharmacist assured us it was the same prescription but simply a generic substitute. We accept generic substitutes on her medications that are not her epilepsy medications to save money. The pharmacist did not alert us the dosage strength was doubled nor was there any sticker or warning label placed on the container alerting us of the doubled change in dosage. Admittedly, we also make a serious mistake by not reading the prescription label which was printed with the correct dosage and instructions. Subsequently that four week

prescription was taken in two weeks. The error only became apparent when the refill was denied by insurance. Subsequently, immediate blood labs and an ultrasound of her organs were ordered and fortunately there was no grave organ damage detected. Had this dosage error occurred to her prescription epilepsy drugs, she would have required emergency hospitalization care due to severe over toxicity and she could have died. I immediately wrote a letter to our pharmacy and hand delivered to them. All five pharmacists know us by name when we come there now.

Because our daughter has a very narrow therapeutic range, we have documented seizures occur more when changed to generic formulas. We'll do whatever it takes and pay whatever the costs to improve her chances to live her life with fewer seizures. We can't tell you how difficult it was to find a local employer who was willing to hire our daughter due to liability of injury and the disruptions that occur when seizures occur while working. It is conditional to her employment that we've committed to be accessible to the store within 5 minutes whenever Katie works there. The Goodwill store doesn't have health care provisions, so we must immediately provide support contingent to her continued employment.

In summary, we need to insure our daughter receives the exact medications that truly work best for her. Our neurologist and our family need to be notified anytime a substitute formulation is dispensed. This bill will provide us with necessary safety as we attempt to maintain balance in our lives. We liken our current lives as walking on a tightrope. We know pharmacies make mistakes as we have experienced in the past.

We're sorry we were unable to make arrangements to attend today's public hearing. Please be clear this does not mean this bill is any less significant to our lives now than it was when we have been present advocating in Madison for passage of this bill in the past. We understand and support the government's need to stop wasteful spending. But laws must protect the health and welfare for those individuals who require exact prescription medications. As parents we hope our daughter has a fair chance to become the best she can be. We are truly grateful for your support in passage of this bill safeguarding substitutions made by pharmacists dispensing epilepsy drugs without prior notifications.

Sincerely,

Laurie and Tom Landgraf
Parents, Legal Guardians and Personal Caregivers of Kathryn Landgraf

Roberta Handley
7537 Lakeview Road
Barneveld, WI 53507

October 20, 2009

Assembly Committee on Public Health
Senate Committee on Health, Health Insurance, Privacy, Property Tax Relief, and Revenue
State Capitol
Room 412 East

Dear Committee Members:

When we lived in Illinois our son Solomon did very well for nearly a year on a brand name drug for his epilepsy, Keppra. We moved to Wisconsin in February of 2009 and with BadgerCare Plus insurance we had to switch Solomon to the generic version, levetiracetam. Within a month he started having seizure activity, which for him means lots of eye blinking and bed wetting episodes.

Our new doctor in Wisconsin decided to try a different drug. They started him on the generic so he wouldn't have to switch later. He did not do well on topiramate alone so lamotrigine was added and later a third drug, ethosuximide. He takes very high doses of his medicines and still cannot seem to get to the levels his doctor wants. Solomon has only gotten back to his good seizure control in the past couple of weeks. We'll never know if he would have had all these problems and all these doctor visits if he had been able to stay on Keppra by itself.

I also want you to know that Solomon is a very bright nine year old who used to get all A's on his spelling tests. Now he seems to have short-term memory problems and attention problems. Homework that should take 15 minutes can take much, much longer for him to finish. The sad thing about this is that we now have three medicines to worry about.

Please support the Epilepsy Patient Protection Bill. It could help other families avoid a similar ordeal.

Sincerely,

Roberta Handley
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